Wnt signaling stimulates ATGL-regulated lipolysis in dermal fibrosis

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Fibrotic disorders, characterized by the deposition of excessive extracellular matrix in all organs and the loss of lipid-filled cells in several organs, contribute to approximately 45% of deaths in Europe and North America. Skin has a distinct dermal white adipose tissue (DWAT) compartment, making dermal fibrosis a good model for studying fibrotic fat loss. DWAT adipocytes perform various functions impacted by their lipid content. A primary process by which adipocytes homeostatically modulate their lipid content and mobilize stored lipid is adipose triglyceride lipase (ATGL)-regulated lipolysis. The mechanisms underlying fibrotic fat loss in DWAT and the impact of lipid depletion in fibrosis are unknown. Wnt signaling is dysregulated in human fibrosis and has known anti-adipogenic roles. We hypothesize that dermal Wnt signaling activation stimulates ATGL-regulated lipolysis leading to fibrotic lipid depletion. Using a genetically inducible and reversible mouse model of dermal Wnt activation, we show Wnt activation is sufficient to cause dermal fibrosis. The ATGL-regulated lipolysis axis is activated in DWAT adipocytes during the onset and progression of Wnt-induced fibrosis. Dermal Wnt activation leads to elevated phosphorylated hormone sensitive lipase (HSL) and phosphorylated perilipin, lipolytic proteins downstream of ATGL, preceding fibrotic fat loss in vivo. Wnt activation also leads to a reduction in the size of perilipin-positive adipocyte lipid droplets in vivo. Thus, stimulated ATGL-regulated lipolysis occurs as an early event in dermal fibrosis. Consistently, murine primary intradermal adipocytes release more glycerol, a product of lipolysis, upon Wnt activation in vitro indicating that Wnt signaling has cell-autonomous lipolytic effects. ATGL enzymatic inhibition is sufficient to rescue Wnt-induced lipolysis. Current studies focus on the role of ATGL in Wnt-induced dermal fibrosis in vivo. Our results implicate lipolysis as a novel therapeutic target for fibrosis treatment.

CO-Detection by indexing (CODEX) reveals clinically distinct classes of eczematous rashes

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Spongiotic rashes are known to be more heterogeneous than psoriasis vulgaris, but a more precise molecular classification has yet to be established. We performed CO-Detection by indexing (CODEX), which utilizes DNA-barcoded antibodies visualized by cyclic addition and removal of fluorescently labeled complementary DNA oligos, to perform highly multiplexed immunofluorescence on 12 samples of histopathologically spongiotic dermatitis, ranging from allergic contact dermatitis to endogenous eczema. This type of systems-level approach utilizing highly multiplexed spatial imaging, which captures many antigens on a single cell basis, has not been previously utilized in spongiotic dermatitis, nor in any other rashes. We utilized a customized 40 antibody panel allowing enumeration of key APC and T cell types while ascertaining immune cell functional states/signaling status and spatial orientation to skin anatomic structures and cell types. We identified recurrently aberrant immune cell subpopulations enabling subclassification of these rashes into distinct classes correlating with etiology and anatomic site ( p < .007). Our findings point to a broadly applicable technology capable of stratifying histopathologically indistinct rashes.

IL-33 signaling in sensory neurons promotes dry skin itch

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Chronic itch is a highly debilitating and often intractable condition that affects up to 20% of the population. Despite recent advances in uncovering the key cellular and molecular pathways that underlie chronic itch, most studies have focused on itch that arises in the setting of inflammatory skin disorders. Thus, how itch is elicited in conditions that lack overt inflammation, such as in dry skin (xerosis) and chronic pruritus of unknown origin (CPUO), remains poorly understood. IL-33 has recently been implicated in a mouse model of dry skin itch. Additionally, we find that patients with CPUO exhibit elevated levels of serum IL-33 compared to control subjects. However, the precise mechanisms by which IL-33 promotes itch remains unclear. Although a well-known driver of cutaneous inflammation, we hypothesized that IL-33 can promote itch independently of immune cells. Indeed, we demonstrate that IL-33 activates sensory neurons from the dorsal root ganglia of mice and humans. Further, in a mouse model of dry skin, we find that both mast cells and lymphocytes are dispensable for the development of chronic itch. Instead, mice that conditionally lack IL-33 receptor (ST2) on sensory neurons exhibit attenuated dry skin itch. Collectively, these findings indicate that sensory neuron-specific IL-33 activity is required in the context of dry skin itch.